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Withholding temozolomide in glioblastoma patients with unmethylated *MGMT* promoter—still a dilemma?

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Ten years ago we established O-6-methylguanine-DNA methyltransferase (*MGMT*) gene promoter methylation as the first predictive marker in neuro-oncology, and the strongest prognostic factor for treatment outcome in patients with newly diagnosed glioblastoma (GBM). But rather than embracing a marker that allows identification and selection of patients likely to derive some benefit from the addition of alkylating agent chemotherapy, we have been challenging the validity of the findings, are still striving for the one perfect molecular test, and are treating the majority of patients with temozolomide (TMZ) chemotherapy irrespective of the tumor's *MGMT* promoter status. Aren't the data convincing enough, or is it because of the lack of effective alternative treatments to be offered to patients with an unmethylated *MGMT* promoter?

Following a large body of mechanistic evidence for the role of *MGMT* in repairing lesions of alkylating agents, *MGMT* expression was advanced as a resistance factor in glioma in the 1990s. Subsequently, seminal work by Esteller and colleagues¹ demonstrated a correlation with promoter methylation of the *MGMT* gene in an analysis of samples from patients in Spain treated with chemotherapy comprising the alkylating agent carmustine (BCNU). We confirmed this observation in an unplanned analysis of patients treated within our phase II trial with upfront TMZ.² Finally, in 2005, our retrospective analysis of prospectively treated patients within a randomized phase III trial demonstrated a clear predictive value of *MGMT* promoter methylation status.³ Since then, numerous additional trials have consistently demonstrated the prognostic effect of the *MGMT* status, but as all patients are now receiving upfront TMZ chemotherapy, the predictive value could not be evaluated again. The one exception is elderly glioblastoma patients in whom the relative benefit of adding chemotherapy is of lesser magnitude. Two randomized trials compared single-agent TMZ chemotherapy versus radiotherapy (RT).^{4,5} In this more fragile patient population it was shown that treating *MGMT* unmethylated tumors with TMZ was detrimental, while patients with methylated tumors fared best if treated with TMZ (even in the absence of RT). These 2 trials confirm the predictive value of the *MGMT* status. Together, the data allow the conclusion

that alkylating agent chemotherapy is of marginal benefit, if any, for patients with *MGMT* unmethylated GBM.

By continuing to treat the majority of *MGMT* unmethylated patients with TMZ, we are missing an opportunity to do better. Innovative treatment approaches with novel agents in combination with RT may provide a better chance for improved outcome than adhering to the use of an agent with marginal activity. From the patient's point of view, it may be perceived as “wasting the last opportunity” to try a potentially efficacious new agent. Clearly, this patient population would benefit most from drugs with other mechanisms of action. To date, only a few trials have selected patients and assigned treatments according to *MGMT* promoter methylation status.^{6–9}

Adding a new drug or agent on top of the previously established combined modality regimen may cause undue toxicity or drug interaction, thus requiring dose reduction and treatment with potentially subtherapeutic doses. As an example, the addition of polyglutamated paclitaxel to the combination of TMZ/RT led to early discontinuation due to prohibitive toxicity,¹⁰ but this resulted in a follow-up trial in *MGMT* unmethylated patients only, omitting TMZ during RT (www.clinicaltrials.gov: NCT01402063). Still, patients with an unmethylated *MGMT* promoter are in greatest need of improved treatments and may benefit from the opportunity to replace TMZ by novel agents. In a randomized European Organisation for Research and Treatment of Cancer (EORTC) trial for patients with an unmethylated *MGMT* promoter only, temsirolimus maintenance and compared with standard TMZ/RT followed by TMZ.⁸ Similarly, Herrlinger and colleagues⁹ randomized patients with an unmethylated *MGMT* promoter to either standard TMZ/RT followed by TMZ or RT combined with irinotecan and bevacizumab followed by maintenance irinotecan/bevacizumab. Although both trials failed to show improved outcome compared with the standard, it is important to note that dropping TMZ was not detrimental (Table 1).

Treatment selection according to a molecular marker is intimately dependent on the validity and reproducibility of the molecular test. Standardizing the *MGMT* assay and determining the

Table 1. Outcome of *MGMT* unmethylated glioblastoma

Trial Name Experimental Regimen	Publication Year/Ref.	Median Overall Survival, mo		
		Standard Arm	Experimental Arm	
		TMZ/RT→TMZ	TMZ/RT + Novel Agent	RT + Novel Agent
EORTC 26981 RT alone	2005 ³	12.6		11.8*
Glarius Beva/RT	2014 ⁹	17.3		16.6
EORTC 26082 Temozolimus	2014 ⁸	16		14.8
CORE Cil (2×/wk)/TMZ/RT→Cil/TMZ	2015 ⁷	13.4	16.3	
Cil (5×/wk)/TMZ/RT→Cil/TMZ			14.5	
RTOG 0525† TMZ/RT→TMZ (21/28d)	2012 ¹⁴	16.6	15.4	
RTOG 0825† Beva/TMZ/RT→beva/TMZ	2014 ¹⁵	14.6	14.0	
AVAglia† Beva/TMZ/RT→beva/TMZ	2014 ¹⁶	16.7	16.8	

Abbreviations: Beva, bevacizumab; cil, cilengitide; RTOG, Radiation Therapy Oncology Group; AVAglio, Avastin in Glioblastoma.

†Subgroup of *MGMT* unmethylated tumors.

*RT alone.

optimal cutoff for outcome prediction have been a challenge. It is obvious that choice of methodology and quantity and quality of the sample may yield different limits of detection and levels of precision for prediction. Of note, unlike a mutation that is present or absent, promoter methylation creates a pattern recognized by so-called methyl-binding proteins, which are relevant for inhibition of expression. These patterns are identified by different means depending on the methodology. This can result in some discrepancies of classification that mostly affect samples with incomplete methylation. As with any test in medicine, however, appropriate validation is required, including but not limited to reproducibility and association with outcome in an independent prospective cohort. Prospective testing in the trials reported earlier has been performed centrally using a quantitative methylation-specific PCR assay that is commercially available.¹¹ In this assay the technical cutoff between methylated and unmethylated was set at the nadir of the bimodal distribution of the methylated *MGMT* measured (ratio with a normalizing gene) in a large population of samples.⁶ Evidently, there is a gray zone around the cutoff that can be approximated by a confidence interval. In 2 of the trials dropping TMZ,^{8,9} the lower boundary of the 95% CI was used to select unmethylated patients (cutoff with a “safety margin”) in order to avoid withholding TMZ from a patient who could potentially profit. The challenges of *MGMT* testing have been reviewed extensively elsewhere.¹²

Additional biomarkers are required for appropriate testing of new targeted drugs allowing for selective enrichment of the potentially sensitive patient population. The frequency of a potentially druggable target, however, may be so low (eg, 3% for fibroblast growth factor receptor 3–transforming acidic coiled-coil protein 3 fusions¹³) that conducting prospective

and controlled clinical trials is practically impossible. Quality assurance and the paucity of material available in the brain require platforms that will provide an array of biomarkers rather than individual tests.

Patients with unmethylated GBM are in need of better treatments. This population not only offers the opportunity to test novel treatments but actually requires—more than other patients—that they be offered innovative therapies right from the diagnosis of GBM. The extended experience of the predictive value of the *MGMT* status in GBM and the reassuring first results from trials selecting patients with unmethylated *MGMT* for experimental therapy omitting TMZ provide sufficient confidence for such an adapted trial design. Recruiting patients according to their *MGMT* status opens opportunities for innovative new therapies not limited by the treatment scheme of TMZ and its toxicity. This will allow us to focus on new drugs that need to be developed together with their corresponding biomarkers.

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